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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/768,193	02/02/2004	Katsuhiko Yanagisawa	040036	3691

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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/768,193	YANAGISAWA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Claims 3-7 have been amended and claims 1-2 and 8-31 have been canceled as requested in the amendment filed on November 30, 2006. Following the amendment, claims 3-7 are pending in the instant application.

2. Claims **3-7** are under examination in the instant office action.

3. Any objection or rejection of record directed to instant claims 1-2 or 8-10 is/are hereby rendered moot in view of Applicant's cancellation of said claims.

Withdrawn Objections and Claim Rejections

4. The objections to the specification regarding sequence requirements and improper characters, as set forth at pp. 2-3 of the previous office action mailed August 3, 2006, are withdrawn in view of Applicant's amendments to the specification.

5. The objection to claims 3-7 as set forth at pp. 3-4 of the previous office action mailed August 3, 2006 is withdrawn in view of Applicant's amendments to the claims.

6. The rejection of claims 3-7 under 35 U.S.C. 112, first paragraph, as set forth at pp. 4-7 of the previous office action (08/03/2006) is withdrawn in view of Applicant's amendments to the claims.

7. The rejection of claims 3-6 under 35 U.S.C. 102(b) as being anticipated by Yanagisawa et al. (*FEBS Lett*ers, 1997; 420: 43-46), as set forth at pp. 8-9 of the previous office action (08/03/2006) is withdrawn in view of Applicant's amendments to the claims.

Maintained and New Claim Objections or Rejections, Necessitated by Amendment

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. The rejection of amended claim 7 under 35 U.S.C. 103(a) as being unpatentable over Yanagisawa et al. (*FEBS Lett*ers, 1997; **420**: 43-46), in view of US Patent No. 5,530,101 to Queen et al., 25 June 1996 and Webber et al. (*Mol Immunol*, 1995; **32**(4): 249-258) is maintained for reasons of record (see previous office action mailed 08/03/2006) and is further applied to amended claims 3-6 for the reasons stated below.

The claims are drawn to an antibody that recognizes GM1 ganglioside-bound amyloid β-protein (GM1/Aβ) and inhibits the formation of amyloid fibrils, wherein the antibody is a recombinant IgG, Fab, Fab', $F(ab')_2$, scFv, or dsFv. The claims are also drawn to a humanized version of this GM1/Aβ antibody.

At pages 11-13 of the response filed November 30, 2006, Applicant recaps the instant invention, emphasizing that the prior art monoclonal 4396 antibody was sequenced and genetically manipulated to obtain a recombinant IgG class antibody, i.e., "antibody 4396C", which Applicant notes falls into the scope of the amended claim 3. Applicant argues that the recombinant antibody's ability to inhibit the formation of amyloid fibrils, "in other words, suppression of Aβ deposition" could not have been anticipated or even obvious to the skilled artisan, because the prior art 4396 antibody, which is IgM class, was only taught to have an affinity toward Aβ bound to lipid vesicles. Applicant therefore asserts that the disclosure by Yanagisawa et al. is not sufficient for making a recombinant IgG class antibody as instantly claimed, nor do the teachings of Queen or Webber correct such deficiency. Applicant thus argues that there is "absolutely no teaching of a *humanized* antibody *being a recombinant IgG, Fab, Fab', $F(ab')_2$, scFv, or dsFv*," comprising SEQ ID NOs: 1-6. Furthermore, Applicant asserts

that because the claimed antibody is an IgG class antibody or a fragment thereof – compared with the 4396 antibody which is IgM class – it advantageously shows a lower activity of non-specific absorption as well as far lower tendency to aggregate, and therefore is much more suitable for diagnostic and therapeutic use. Because there is no suggestion of this in the combination of references, Applicant argues, there is no motivation in the references for using an IgG class antibody.

Applicant's arguments filed November 30, 2006 have been fully considered but they are not persuasive. First it is noted that the addition of "recombinant IgG" in amended claim 3 is recited in the alternative, i.e., "the antibody is a recombinant IgG, Fab, Fab', $F(ab')_2$, scFv, ***or*** dsFv" (emphasis added), meaning that the claimed antibody can belong to the IgG class *or* it may instead be an antigen binding fragment of non-specified immunoglobulin class *or* it may be a single chain antibody of non-specified immunoglobulin class. The humanized antibody of claim 7 would therefore be a humanized version of any of the above – a humanized IgG antibody, a humanized antigen binding fragment (e.g., Fab, Fab', $F(ab')_2$), or a humanized single chain antibody (e.g., scFV or dsFv). It is also noted that Fab, Fab', and $F(ab')_2$ antibody fragments are derived by enzymatic cleavage and lack the "stem" of the antibody, or the constant regions, which define the immunoglobulin class and mediate the effector functions associated with the class of immunoglobulin. Thus, an antibody-binding fragment can never be of a particular immunoglobulin class.

As stated previously, the 4396 antibody taught by Yanagisawa et al. would inherently comprise **all** of the heavy and light chain CDRs (SEQ ID NOs: 1-6) instantly

claimed, including the heavy chain variable region of SEQ ID NO: 7 and light chain variable region of SEQ ID NO: 8, **regardless** of its particular immunoglobulin class. Therefore, antibody binding fragments and single chain antibodies derived from the humanized version of the 4396 antibody of instant claim 7 would still be obvious in view of the combined teachings of all of the references. Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). A humanized antibody comprises an acceptor human framework with mouse monoclonal heavy and light chain variable regions comprising the CDRs grafted into the acceptor framework. As the CDRs of the prior art 4396 antibody are the same as the instantly claimed CDRs (as evidenced, for example, in the instant specification at p. 14, line 12 – p. 15, line 13), the CDR-grafted humanized antibody binding fragments and humanized single chain antibodies made by the combined teachings discussed above would be the same as instantly claimed and thus would be inherently capable of inhibiting amyloid fibril formation.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re*

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Yanagisawa et al. explicitly teach that the 4396 monoclonal antibody may be useful as a probe to gain insight into the initial molecular mechanism of Aβ deposition, including the generation of GM1 ganlioside-bound amyloid-β (GM1/Aβ), in the brains of patients with Alzheimer's disease (see p. 46, bottom of 1st column). Thus, Yanagisawa teaches that the 4396 antibody, which is a mouse monoclonal antibody, would be diagnostically useful. Queen teaches that non-human monoclonal antibodies contain substantial stretches of amino acid sequences that are immunogenic when injected into a human patient (see column 1, lines 41-44). Queen also discloses that humanized antibodies are substantially non-immunogenic in humans yet retain substantially the same affinity as the donor immunoglobulin to the antigen (see Abstract). Therefore, one of skill in the art would be motivated to make a humanized 4396 antibody to use diagnostically in administration to patients with Alzheimer's disease.

Queen also teaches the production and use of antigen binding fragments and single chain antibodies (see column 11, lines 25-28, and column 17, lines 31-60). Webber teaches that because of their small size, single chain antibodies (scFvs) are useful as probes because they have superior tissue penetration and are cleared quickly from the circulation (p. 249, 2nd paragraph). In addition, Webber teaches that dsFv molecules are even more valuable than scFVs as probes because the disulfide bonds make dsFvs more stable and capable of being produced in greater quantities than scFv molecules, and dsFvs retain affinity for antigen equivalent to the parent IgG molecule. Accordingly, the skilled artisan would have ample motivation to make, for example,

single chain antibodies (scFV or dsFV) from the parent 4396 antibody or humanized antigen binding fragments (Fab, Fab', or $F(ab')_2$), scFVs or dsFVs of the 4396 antibody for diagnostic use, particularly with regard to diagnostics associated with Alzheimer's disease, because such molecules would be less immunogenic and/or more quickly cleared than the non-human monoclonal antibody from which they are derived. Thus, the combined teachings of the above references render obvious instant claims 3-7.

10. Claims 3-7, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanagisawa et al. (*FEBS Lett*ers, 1997; **420**: 43-46), in view of US Patent No. 5,530,101 to Queen et al., 25 June 1996 and Webber et al. (*Mol Immunol*, 1995; **32**(4): 249-258) as discussed above, and further in view of EP 0 620 276 A1 by Adair et al., published October 19, 1994.

The claims are drawn to an antibody that recognizes GM1 ganglioside-bound amyloid β-protein (GM1/Aβ) and inhibits the formation of amyloid fibrils, wherein the antibody is a recombinant IgG, Fab, Fab', $F(ab')_2$, scFv, or dsFv. The claims are also drawn to a humanized version of this GM1/Aβ antibody.

The teachings of Yanagisawa, Queen, and Webber are discussed *supra*.

The teachings of Adair are cumulative with those of Queen, disclosing humanization of monoclonal antibodies. However, Adair additionally teaches that the constant region domains of CDR-grafted humanized antibodies may be selected with regard to the proposed function of the antibody, in particular the effector functions, which may be required. For example, Adair discloses that the constant region domains

of the human acceptor framework may be human IgA, IgE, IgG or IgM domains. Further, Adair teaches that "[i]n particular, IgG human constant region domains may be used, especially of the IgG1 and IgG3 isotypes, when the humanized antibody molecule is intended for therapeutic uses, and antibody effector functions are required. Alternatively, IgG2 and IgG4 isotypes may be used when the humanized antibody molecule is intended for therapeutic purposes and antibody effector functions are not required, e.g. for simple blocking of lymphokine activity" (see paragraph spanning pp. 6-7). Therapeutic and diagnostic compositions comprising these CDR-grafted humanized antibodies are disclosed (see claims 22-23). Adair thus teaches selection of an IgG human constant region for the acceptor framework for production of humanized antibodies, particularly when therapeutic or diagnostic uses are desired.

Accordingly, it would have been obvious to one of skill in the art at the time the invention was filed to make a recombinant IgG humanized 4396 antibody, or antigen binding fragments or single chain antibodies thereof, as taught by the combination of references. The skilled artisan would be motivated to make such a selection because Adair teaches that the constant region domains of the humanized antibody may be selected for with regard to the desired use, and that human IgG domains such as IgG1, IgG2, IgG3 or IgG4 are particularly preferred if the intended use of the antibody is for therapy or diagnosis in a human patient. The skilled artisan would have a reasonable expectation that such antibodies could be successfully produced based on the teachings of Adair and Queen, demonstrating the production of CDR-grafted humanized

antibodies (see Examples for each reference). As such, instant claims 3-7 would be rendered obvious in view of the combined references.

Claim Objections

11. Claim 3 is objected to because of the following informalities: the claim language used to define the antibody, i.e. "the antibody is...", is considered non-conventional. The Examiner suggests addition of the word "wherein" to the above phrase, i.e., "wherein the antibody is..." to negate the objection. Appropriate correction is required.

Conclusion

12. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Kimberly Ballard, Ph.D.
February 7, 2007

ELIZABETH KEMMERER
PRIMARY EXAMINER